

Claims

Please cancel claims 7 and 54 without prejudice and amend the claims as follows:

1. (Currently Amended) A computer-implemented method for quantifying relative gene relatedness for a plurality of candidate genes for which a plurality of gene expression level observations have been collected, the method comprising:

for a predicted gene selected from the candidate genes, selecting a plurality of selected permutations subset combinations of the plurality of candidate genes, and performing (a)-(c) for each subset combination to generate a plurality of quantifications of relative relatedness for the predicted gene and the subset combinations:

(a) based on data comprising the plurality of gene expression level observations for the plurality of candidate genes, constructing a nonlinear model predicting gene expression for the predicted gene, wherein the nonlinear model accepts gene expression levels for the permutation subset combination of the plurality of candidate genes as inputs and produces a gene expression level for the predicted gene as an output;

(b) predicting gene expression of the predicted gene with the nonlinear model; and

(c) measuring effectiveness of the nonlinear model in accurately predicting the gene expression level of the predicted gene as compared to the gene expression level observations, the effectiveness being a quantification of relative gene relatedness ~~for~~ of the predicted gene and the plurality of candidate genes of the permutation subset combination of the plurality of candidate genes with respect to other subset combinations of the candidate genes ; and

presenting a ranked plurality of the plurality of quantifications of ~~gene-relatedness~~ showing relative gene relatedness for a plurality of the permutations subset combinations of the candidate genes.

2. (Original) A computer-readable medium comprising computer-readable instructions for performing the method of claim 1.

3. (Original) The method of claim 1 wherein the nonlinear model accepts a plurality of predictive elements as inputs, wherein at least one of the predictive elements indicates whether a gene expression observation is associated with having applied a particular external stimulus to biological material.

4. (Currently Amended) The method of claim 1 ~~wherein~~ further comprising:
accepting by the nonlinear model ~~accepts~~ a plurality of predictive elements as inputs, wherein at least one of the predictive elements indicates whether a gene expression observation is associated with a particular cell state.

5. (Currently Amended) The method of claim 1 ~~wherein~~ further comprising:
accepting by the nonlinear model ~~accepts~~ a plurality of predictive elements as inputs, wherein at least one of the predictive elements indicates differential gene expression between two samples of biological material.

6. (Original) The method of claim 1 wherein the nonlinear model comprises a multivariate prediction function accepting two or more inputs to predict gene expression.

7. (Canceled) The method of claim 1 wherein measuring effectiveness of the nonlinear model comprises comparing observed gene expression to gene expression predicted by the nonlinear model.

8. (Original) The method of claim 1 wherein constructing the nonlinear model predicting gene expression comprises choosing a nonlinear model from a constrained set of nonlinear models.

9. (Original) The method of claim 1 wherein measuring the model's effectiveness comprises evaluating the model to estimate a coefficient of determination for an optimal model estimated by the model.

10. (Original) The method of claim 1 wherein the nonlinear model predicting gene expression is a full-logic model predicting gene expression for a predicted candidate gene, and the effectiveness of the model is measured by comparing predictions of gene expression for the predicted candidate gene by the model with observations of gene expression for the predicted candidate gene.

11. (Currently Amended) The method of claim 1 further comprising:
obtaining ~~the data comprising~~ the plurality of gene expression level observations from results of a plurality of cDNA microarray experiments measuring mRNA transcription levels for a plurality of genes in biological material.

12. (Original) The method of claim 1 wherein the data comprising a plurality of gene expression observations is divided into a training set of data and a test set of data, wherein the nonlinear model predicting gene expression is generated via the training set data; and effectiveness of the nonlinear model is measured via the test set of data.

13. (Original) The method of claim 12 wherein the training set of data is extended by randomly reordering and recycling gene expression observations.

14. (Original) The method of claim 1 wherein
a plurality of training data sets are repeatedly chosen from the data comprising a plurality of gene expression observations;

the nonlinear model is one of a plurality of models constructed from the plurality of training data sets; and

quantification of the relatedness for the plurality of candidate genes is measured by measuring average effectiveness of the plurality of models constructed from the plurality of training data sets.

15. (Currently Amended) The method of claim 1 further comprising:
to determine contribution of a predictive element to the quantification of relatedness,
constructing an additional nonlinear model predicting gene expression, wherein the additional
nonlinear model has the predictive element as a single input, and measuring the effectiveness
of the additional nonlinear model.

16. (Original) The method of claim 1 wherein the nonlinear model predicting
gene expression is a truth table predicting a gene expression level for a predicted candidate gene
from predictive elements comprising expression level observations for candidate genes other
than the predicted candidate gene.

17. (Original) The method of claim 16 wherein the truth table comprises ternary
discrete values.

18. (Original) The method of claim 16 wherein gene expression levels in the truth
table are ternary discrete values.

19. (Original) The method of claim 16 wherein
the truth table comprises a plurality of rows for possible combinations of expression level
observations for the candidate genes other than the predicted candidate gene; and
for at least one of the rows, the truth table indicates predicted gene expression for the
predicted candidate gene with a thresholded weighted average of gene expression level
observations associated with the row.

20. (Original) The method of claim 1 wherein the nonlinear model predicting
gene expression is a neural network predicting gene expression.

21. (Original) The method of claim 20 wherein the neural network consists of
one neuron which predicts a gene expression level for a single predicted candidate gene.

22. (Original) The method of claim 21 wherein the neuron is a ternary perceptron accepting predictive elements as inputs, wherein the predictive elements comprise gene expression levels indicated as one of three possible values: up, unchanged, and down.

23. (Original) The method of claim 22 further comprising:
displaying a three-dimensional graph representing the ternary perceptron with two planes separating points on the graph into points relating to like predicted values.

24. (Original) The method of claim 22 further comprising:
displaying a three-dimensional graph representing the ternary perceptron with objects at points in three-dimensional space within the graph, wherein axes of the graph relate to thresholded gene expression levels for three of the candidate genes.

25. (Original) The method of claim 24 wherein the objects are of a color indicating a predicted gene expression level.

26. (Original) The method of claim 24 wherein the objects are of a size indicating a number of observations related to a point on the graph.

27. (Original) The method of claim 1 wherein the data comprising a plurality of gene expression observations comprises gene expression level observations generated by subjecting sample biological material to an experimental condition and observing regulation of mRNA transcription levels for a plurality of genes in the biological material as a result of being subjected to the experimental condition.

28. (Original) The method of claim 27 wherein the data comprising a plurality of gene expression observations further comprises an indication of the experimental condition to which the biological material related to an observation was subjected and the indication is included in the model to predict gene expression.

29. **(Currently amended)** A computer-implemented method for identifying genes related to a target gene by analyzing gene expression level observations for the genes, the method comprising:

based on the gene expression level observations, constructing multivariate nonlinear predictors that predict an expression level for the target gene, wherein the predictors accept gene expression levels for other genes as predictive elements;

estimating a coefficient of determination for sets of predictive elements and the target gene by comparing results of the multivariate nonlinear predictors with gene expression level observations for the target gene, wherein the predictive elements comprise expression level observations for **groups of** genes other than the target gene; and

ranking the groups of genes other than the target gene by coefficient of determination to present the **groups of** genes other than the target gene in order of likelihood of relatedness to the target gene.

30. **(Original)** The method of claim 29 further comprising:

indicating a proper subset of the genes having the highest likelihood of relatedness to the target gene.

31. **(Original)** A computer-implemented method for analyzing gene expression level observations for a set of genes comprising a target gene, the method comprising:

estimating a coefficient of determination for an optimal multivariate nonlinear model predicting gene expression of the target gene by constructing a multivariate nonlinear model from the gene expression level observations of gene expression for the target gene, wherein the optimal multivariate nonlinear model and the constructed multivariate nonlinear model predict gene expression of the target gene based on variables representing gene expression levels of genes other than the target gene.

32. **(Original)** The method of claim 31 wherein the optimal multivariate nonlinear model and the constructed multivariate nonlinear model predict gene expression based, at least in part, on inputs comprising an indication of a condition to which biological material relating to the observations has been subjected.

33. **(Currently Amended)** A method for identifying related genes out of a set of genes for which gene expression level observations have been collected, the method comprising:

for at least one predicted gene out of the set of genes, training an artificial intelligence function to predict gene expression for the predicted gene, wherein the artificial intelligence function takes one or more predictive elements as inputs and produces a gene expression level for the predicted gene as an output, wherein at least one of the predictive elements is a gene expression level for a gene other than the predicted gene; **and**

testing effectiveness of the artificial intelligence function in predicting expression of the predicted gene to rate relative relatedness of the predicted gene and at least one gene associated with the predictive elements; **and**

presenting the relative relatedness in a computer user interface showing a ranking of relative relatedness for a plurality of gene groups.

34. **(Original)** The method of claim 33 wherein the artificial intelligence function takes a plurality of predictive elements as inputs.

35. **(Original)** The method of claim 33 wherein the predictive elements comprise a variable indicating biological material was subjected to an experimental condition.

36. (Original) For a plurality of observed genes for which expression levels have been observed, a method of presenting an analysis of the expression levels to assist in identifying related genes, the method comprising:

denoting a particular observed gene as a predicted gene;
for the predicted gene, constructing a plurality of nonlinear multivariate models predicting expression of the observed gene, wherein the nonlinear multivariate models comprise a variety of predictive elements chosen from permutations of expression levels of observed genes other than the predicted gene;
measuring effectiveness of the nonlinear multivariate models in predicting expression of the predicted gene to quantify relatedness between the predicted gene and the set of genes associated with the predictive elements of the models; and
presenting a quantification of relatedness between the predicted gene and a set of genes associated with the predictive elements of at least one of the models.

37. (Original) The method of claim 36 further comprising:
for a set of predictive elements and a predicted gene, displaying a graph indicating the amount of increase in the effectiveness of the model for each of the predictive elements.

38. (Original) The method of claim 36 wherein at least two of the plurality of nonlinear multivariate models predicting expression of the observed gene are implemented in specialized hardware circuits for predicting gene expression.

39. (Original) The method of claim 36 further comprising:
displaying a user interface for evaluating the analysis, wherein the user interface comprises display elements graphically indicating the relatedness of the predicted gene to a plurality of gene sets.

40. (Original) The method of claim 39 further comprising:
displaying only those display elements indicating sets of genes in which each gene in the set improves the relatedness.

41. (Original) The method of claim 39 further comprising:
accepting as input a set of one or more designated predictor genes;
accepting as input a threshold relatedness;
accepting as input a set of one or more designated predicted genes; and
limiting the display elements of the user interface to those sets of genes having as
members the one or more designated predictor genes and having at least the threshold relatedness
for the one or more designated predicted genes.

42. (Original) The method of claim 39 further comprising:
accepting as input a set of one or more designated predictor genes; and
limiting display elements of the user interface to those sets of genes having the one or
more designated predictor genes.

43. (Original) The method of claim 42 further comprising:
accepting as input a threshold increase in relatedness; and
further limiting display elements of the user interface to those sets of genes for which
addition of the one or more designated predictor genes increases the relatedness by at least the
threshold increase in relatedness.

44. (Original) The method of claim 36 further comprising presenting a ranking of
gene sets according to their relatedness, wherein the ranking indicates which genes are in the
sets.

45. (Original) The method of claim 44 wherein the ranking further indicates
contribution of individual predictive elements to the effectiveness of the models.

46. (Original) The method of claim 36 wherein the predictive elements comprise
a variable indicative of whether biological material related to a gene expression observation has
been subjected to a particular condition.

47. (Currently Amended) For a plurality of observed genes for which expression levels have been observed, a method of performing an analysis of the expression levels to assist in identifying related genes, the method comprising:

(a) for a plurality of the observed genes, denoting a particular observed gene as a predicted gene and performing at least (b) and (c);

(b) for the predicted gene, constructing a plurality of nonlinear multivariate models predicting expression of the predicted gene, wherein the nonlinear multivariate models have a variety of predictive elements chosen from permutations of expression levels of observed genes other than the predicted gene;

(c) measuring effectiveness of the nonlinear multivariate models in predicting expression of the predicted gene to provide a quantification of relative relatedness between the predicted gene and genes associated with the predictive elements of the models.

48. (Original) The method of claim 47 further comprising:
skipping designating genes having fewer than a defined number of changes in expression level as predicted genes.

49. (Original) The method of claim 47 further comprising:
displaying a user interface comprising display elements indicating gene relatedness for a plurality of genes associated with the predictive elements for a plurality of predicted genes.

50. (Previously Presented) A system for quantifying gene relatedness for a plurality of candidate genes for which a plurality of gene expression level observations have been collected, the system comprising:

means for constructing a nonbinary, nonlinear model predicting gene expression based on data comprising the plurality of gene expression level observations for the plurality of candidate genes;

means for predicting gene expression with the nonbinary, nonlinear model; and

means for measuring effectiveness of the nonbinary, nonlinear model in predicting gene expression, the effectiveness indicating gene relatedness for the plurality of candidate genes.

51. (Original) The method of claim 50 wherein the means for predicting gene expression is a specialized hardware circuit.

52. (Original) The method of claim 50 wherein the means for predicting gene expression is a decision tree.

53. (Original) The method of claim 50 wherein the means for predicting gene expression is a truth table chosen from a constrained set of truth tables.

54. (Canceled) A system for quantifying the relatedness of a set of genes, the system comprising:

a multivariate nonlinear predictor constructor operable to construct a multivariate nonlinear predictor based on gene expression level observations for a plurality of candidate genes;

a multivariate nonlinear predictor tester operable to test the effectiveness of the multivariate nonlinear predictor by generating a quantification

a results presenter to present the quantification as indicating relatedness for the plurality of candidate genes.

55. (Canceled)

56. (Canceled)

57. (Canceled)

58. (Canceled)

59. (Canceled)

60. (Canceled)

61. (Currently Amended) A computer-implemented method of ranking the relatedness of a plurality of genes based on gene expression level observations associated with the plurality of genes, the method comprising:

based on the gene expression level observations, constructing a plurality of multivariate nonlinear predictors to predict the expression of a plurality of target genes out of the genes, wherein the multivariate nonlinear predictors comprise predictive elements comprising an observed gene, thereby associating the multivariate nonlinear predictor with the target gene and at least one observed gene;

testing effectiveness of the plurality of multivariate nonlinear predictors in predicting gene expression to quantify relative gene relatedness between the genes associated with the predictors by estimating a coefficient of determination; and

displaying a ranked list of relative gene relatedness among the genes as determined by testing the plurality of multivariate nonlinear predictors.

62. (Previously Presented) The method of claim 1 wherein the gene relatedness indicates relatedness within a network controlling gene expression.

63. (Previously Presented) The method of claim 1 wherein the gene relatedness indicates relatedness based on chains of interaction among various mechanisms.

64. **(Currently Amended)** A computer-implemented method for analyzing a plurality of candidate genes for which a plurality of gene expression level observations have been collected to determine which out of the genes are more related, the method comprising:

for a plurality of selected permutations of the plurality of candidate genes, performing
(a)-(c) for each permutation:

(a) based on data comprising the plurality of gene expression level observations for the plurality of candidate genes, constructing a nonlinear model predicting gene expression for the permutation of the plurality of candidate genes;

(b) predicting gene expression with the nonlinear model; and

(c) measuring effectiveness of the nonlinear model in predicting gene expression, the effectiveness being a quantification of indicating relative gene relatedness for the plurality of candidate genes of the permutation; and

presenting at least one of the permutations of genes as related and ~~a rating indicating an~~
indication of the quantification indicating relative gene relatedness for the permutation at
least one of the permutations.

65. **(Previously Presented)** The method of claim 64 wherein the gene relatedness indicates relatedness within a network controlling gene expression.

66. **(Previously Presented)** The method of claim 50 further comprising:
means for presenting the effectiveness as indicating relatedness for the plurality of candidate genes.

67. **(Previously Presented)** The method of claim 50 wherein the nonlinear model comprises a ternary model.

68. (New) A computer-implemented method comprising:
for a given predicted gene, computing a coefficient of determination for possible combinations of respective predictive elements, wherein the respective predictive elements comprise observed gene expression levels for genes, thereby generating a plurality of coefficients of determination; and
in a computer user interface, presenting ranked indications of the coefficients of determination and indications of gene names for the genes of the respective predictive elements.

69. (New) The method of claim 68 further comprising:
in the computer user interface, indicating a contribution to a coefficient of determination of a predictive element out of the predictive elements.

70. (New) The method of claim 69 wherein
at least one coefficient of determination is presented as a graphical bar; and
the contribution is indicated via denoting a portion of the bar as associated with the predictive element.